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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JIANG, SHAOJIA ANNA	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,593	FRIEDHOFF ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004 and 11 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-16 and 41-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8, 10-16 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on September 23, 2004 wherein claims 2 and 9 are cancelled and claims 1, 3-8, and 10-16 have been amended; claims 41-45 are newly submitted. Claims 17-40 have been cancelled previously.

Currently, claims 1, 3-8, 10-16 and 41-45 are pending in this application.

Claims 1, 3-8, 10-16 and 41-45 as amended now are examined on the merits herein.

The following is new rejection(s) necessitated by Applicant's amendment filed on September 23, 2004.

Moreover, the following new rejection(s) are necessitated by Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on August 11, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 12-16 and 41-45 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for

the particular agents such as HMG-COA reductase inhibitor selected from the group consisting of mevastatin, pravastatin, simvastatin, atolwastatin, lovastatin, rivastatin, fluvastatin disclosed in the specification (see page 51-59) employed in methods for treatments of Alzheimer's disease, does not reasonably provide enablement for the employment any HMG-COA reductase inhibitors, to be administered for the claimed methods of the particular treatments herein, i.e., Alzheimer's disease in a patient.

These recitations, "an HMG-COA reductase inhibitor", in these claims, are seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to in methods for treatments of Alzheimer's disease in a patient.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on any HMG-COA reductase inhibitors, employed in the claimed methods of particular treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "an HMG-COA reductase inhibitor", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular statins for the claimed method of treatment herein (see the specification).

Thus, the instant specification fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice

the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treatments of Alzheimer's disease in a patient, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compounds or their *combination* of represented by "an HMG-COA reductase inhibitor", and while the patient

also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only particular HMG-CoA reductase inhibitor, lovastatin, is employed in working examples of the specification. Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any

compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of any compounds having the function recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Response to Argument

Applicant's arguments filed August 11, 2004 with respect to this rejection made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement have been fully considered but are not deemed persuasive as further discussed below.

Applicant arguments that "the term HMG CoA reductase inhibitor is not merely functional language, but is representative of a known class of drug with an art recognized mechanism of action...", have been considered but not found convincing.

In this case, the instant claims are **not** limited to those particular known HMG-CoA reductase inhibitors in the specification, given their broadest reasonable interpretation. The functional recitation "HMG CoA reductase inhibitor" may reasonably encompass those known and **unknown** or **future known** compounds having the recited functions as of the instant filing date. Note that those **future known** compounds have not yet been discovered and/or made as of the instant filing date. Hence, those unknown or future known compounds encompassed by claim 1 herein **must** require to additional or future research to discover, establish, make and/or verify their usefulness.

It is noted that only a single HMG-CoA reductase inhibitor, lovastatin, is employed in working examples of the specification. Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of any compounds having the function recited in the instant claims suitable to practice the claimed invention, given the fact that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

For the above stated reasons, said claims are properly rejected made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-8, 10-16 and 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scolnick (WO 95/06470, of record) in view of Applicant's admission regarding the prior art in the specification (see page 7-8).

Scolnick discloses methods of treating Alzheimer's disease or the onset of Alzheimer's disease in a human patient comprising administering to the said patient a therapeutically effective amount of a composition comprising an HMG-CoA reductase inhibitor, such as lovastatin, simvastatin, pravastatin, and fluvastatin. Scolnick also discloses that the HMG-CoA reductase inhibitor is administered by a controlled release dosage form.

Scolnick discloses that the range of the therapeutically effective amount of the HMG-CoA reductase inhibitor to be administered per day is about 1-1000 mg, preferably 5-100 mg, e.g., 20 mg/day of lovastatin (see page 11 line 13-15 and Example 1; claims 7-8 and 19-20 in particular). Scolnick discloses that a drug that affects brain vasculature is useful in methods of treating Alzheimer's disease as well. See abstract, page 2 lines 16-20, page 10, and claims 1-25.

Scolnick does not expressly disclose the employment of the art recognized assay selected from the group consisting of radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, western blots, protein A immunoassays, and immtmoelectro-phoresis assays, and combination thereof, to detect Aβ levels in the patient.

However, Applicant's admission regarding the prior art at page 7-8 of the specification teaches:

"Any procedures known in the art for the measurement of β-amyloid levels can be used in the practice of the instant invention. Such procedures include but are not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assâys, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, western blots, protein A immunoassays, and immurpelectro-phoresis assays, combinations thereof and the like." (see page 7, the 3rd paragraph, emphasis added).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the art recognized assay such as ELISA to detect Aβ levels in the patient in a method of managing a patient with Alzheimer's disease.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the art recognized assay such as ELISA to detect Aβ levels in the patient in a method of managing a patient with Alzheimer's disease, since the assay herein is known in the art and art recognized as Applicant admits. Moreover, the employment of these known assay is considered well within conventional skills in the art.

Scolnick does not also expressly disclose that the effective amount of HMG-CoA reductase inhibitor is from about 0.2-10 mg/Kg/day, or up to 240 mg/day, or about 10-120 mg/day, 10-60 mg/day.

Note that since a standard person weight is 70 kg, the range of effective amounts of HMG-CoA reductase inhibitor is 0.2 mg/kg X 70 kg =14 mg to 10 mg/kg X 70 kg = 700 mg.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine or optimize the effective amount of HMG-CoA reductase inhibitor to about 0.2-10 mg/Kg/day (14-700 mg/day), or up to 240 mg/day, or about 10-120 mg/day, 10-60 mg/day, since the claimed ranges herein overlap or lie inside ranges disclosed by Scolnick, about 1-1000 mg, preferably 5-100 mg, e.g., 20 mg/day of lovastatin. Thus, a *prima facie* case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See also MPEP 2144.05.

Response to Argument

Applicant's arguments filed August 11, 2004 with respect to the rejection made under 35 U.S.C. 103(a) as being unpatentable of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant argues that Scolnick fails to recognize and provides no information regarding the level of Aβ being useful as an indicator as to the progression of Alzheimer's disease. Therefore, Scolnick fails in the very least to teach, hint, or suggest tçdetecting a level of Aβ in a body fluid of said patient to determine the efficacy of said HMG COA reductase inhibitor" as recited in the present claims.

Applicant's argument is not found convincing, since the level of Aβ being useful as an indicator as to the progression of Alzheimer's disease is related to the mechanism of action of a treatment. Note that the mechanism of action of a treatment, e.g., lowering level of Aβ, does not have a bearing on the patentability of the invention if the method steps, i.e., , administering the same compound in the same amount to the same or similar patient population, are already known even though applicant has proposed or claimed the mechanism. Applicant's recitation of a new mechanism of action for the prior art method will not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

It must be recognized that any judgment on obviousness takes into account knowledge which was generally available and within the level of ordinary skill at the time the claimed invention was made. In this case, it is known at or before the time the

claimed invention was made, that the increase of Aβ peptide is associated with AD, as Applicant clearly acknowledges and admits by citing other's work or inventions, in the "Background of Invention" of the specification at page 3, 2nd paragraph.

Therefore, detecting a level of Aβ level in order to diagnosis a patient having AD by using these known assay is considered well within conventional skills in the medical art. The claimed invention is clearly obvious in view of the prior art.

Claims 1, 3-8, 10-16 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yankner et al.(WO 99/48488, PTO-1449 submitted August 11, 2004) in view of Applicant's admission regarding the prior art in the specification (see page 7-8).

Yankner discloses that HMG-CoA reductase inhibitor, such as lovastatin, simvastatin, pravastatin, and fluvastatin, are useful in methods of treating Alzheimer's disease (AD) or at risk of developing AD in a human patient by decreasing β-amyloid levels, and methods for predicting or diagnosis AD (see abstract, page 2-4, in particular page 3 line 20-23; Examples at page 6-9; claims 1-20.

Yankner does not expressly disclose the employment of the art recognized assay selected from the group consisting of radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, western blots, protein A

immunoassays, and immtmoelectro-phoresis assays, and combination thereof, to detect Aβ levels in the patient.

Applicant's admission regarding the prior art at page 7-8 of the specification has been discussed above.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the art recognized assay such as ELISA to detect Aβ levels in the patient in a method of managing a patient with Alzheimer's disease.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the art recognized assay such as ELISA to detect Aβ levels in the patient in a method of managing a patient with Alzheimer's disease, since the assay herein is known in the art and art recognized as Applicant admits. Moreover, the employment of these known assay is considered well within conventional skills in the art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on August 11, 2004 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
December 15, 2004